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⑫

## EUROPEAN PATENT APPLICATION

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㉓ Use of 4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives in the treatment of psychosis,  
inflammation, stroke and as immunosuppressants.

㉔ 4-Phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives have been found useful for the treatment of  
psychosis, inflammation, stroke and as immunosuppressants.

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**USE OF 4-PHENYL-1,2,3,4-TETRAHYDRO-1-NAPHTHALENAMINE DERIVATIVES IN THE TREATMENT OF PSYCHOSIS,**

**INFLAMMATION, STROKE AND AS IMMUNOSUPPRESSANTS**

The present invention relates to the use of 4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives in the treatment of psychosis, inflammation, stroke and as immunosuppressants

United States Patent No. 4,536,518 discloses cis-4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives useful as antidepressants.

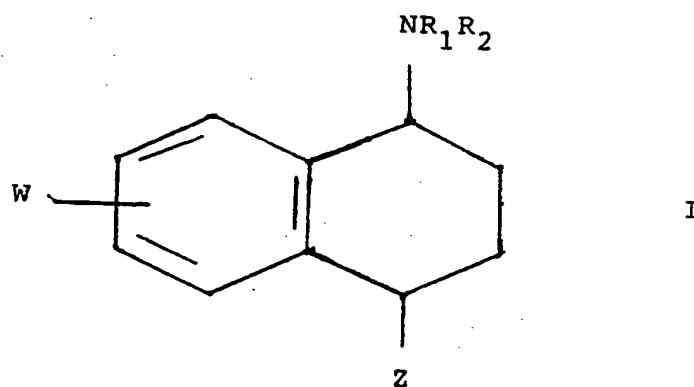
United States Patent No. 4,556,676 discloses trans-4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives useful as antidepressants.

It has now been discovered that the compounds disclosed in the aforementioned United States patents have sigma receptor binding activity and are therefore useful in the treatment of psychosis, inflammation and as immunosuppressants.

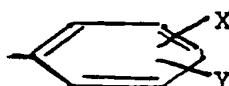
In view of the dissimilar causes of depression and psychosis, the antipsychotic activity of the present compounds could not have been predicted.

Another utility of the present compounds because of their high affinity for sigma receptors is in the treatment of stroke.

The present invention relates to the use of a compound of the formula:



35 or of a pharmaceutically acceptable acid addition salt thereof, wherein R<sub>1</sub> and R<sub>2</sub> are each independently selected from hydrogen and C<sub>1</sub>-C<sub>3</sub> alkyl; Z is



45 wherein X and Y are each independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl, alkoxy of from 1 to 3 carbon atoms and cyano, with at least one of X and Y other than hydrogen; and

50 W is selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl and alkoxy of from 1 to 3 carbon atoms, for the manufacture of a medicament for the treatment of psychosis, inflammation and stroke and for use as an immunosuppressant.

The compounds of the formula 1 include both the cis and the trans isomers. In the cis isomer, the NR<sub>1</sub>R<sub>2</sub> and Z moieties are both oriented on the same side of the cyclohexane ring. In the trans isomer, the NR<sub>1</sub>R<sub>2</sub> and Z moieties are oriented on opposite sides of the cyclohexane ring. Because both the 1 and 4 carbons of Formula 1 are asymmetrically substituted, each cis compound and each trans compound has

two optically active enantiomeric forms denoted, respectively, cis -(1R) and cis -(1S) and trans - (1R) and trans - (1S). The preponderance of the pharmaceutical activity of the cis-isomer compounds of the formula I resides in the (1S)-enantiomeric forms thereof, while the preponderance of pharmaceutical activity of the trans-isomer compounds of formula 1 resides in the (1S)-enantiomeric forms.

5 Preferred compounds or their pharmaceutically acceptable acid addition salts for use in the present invention are:

Cis (1S) (4S)-N-methyl-4-(3,4 -dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;  
 Cis (1S) (4S)-N-methyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;  
 Cis (1S) (4S)-N-methyl-4-(3-trifluoromethyl-4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;  
 10 Trans (1S) (4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;  
 Trans (1R) (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;  
 Cis -(1R) -(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine;  
 Cis (1S) (4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; and  
 Cis (1S) (4S)-N,N-dimethyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

15 The compounds of the formula I or the pharmaceutically acceptable acid addition salts thereof may be prepared and formulated as described in United States Patents 4,556,676 and 4,536,518, the disclosures of which are hereby incorporated herein by reference.

The compounds of the formula I or the pharmaceutically acceptable acid addition salts thereof are useful in treating psychotic disorders in mammalian subjects (e.g. humans). More specifically the present 20 compounds are of use in the treatment of schizophrenia, delusional disorder, brief-reactive psychosis, schizo-effective disorder, atypical psychosis, mania and in emotion discontrol in dementia. For example, the compounds or salts are useful in treating psychotic disorders of the schizophrenic types, and especially for removing or ameliorating such symptoms and conditions as anxiety, agitation, tension, excessive aggression and social and/or emotional withdrawal, etc. that one normally encounters when dealing with psychotic 25 patients.

The compounds of the formula I or the pharmaceutically acceptable salts thereof are also useful in treating inflammatory disorders in mammals (e.g. humans), including psoriasis, arthritis and inflammatory based diseases.

The compounds of the formula I or the pharmaceutically acceptable salts thereof are also useful as 30 immunosuppressants.

The compounds of the formula I or the pharmaceutically acceptable salts thereof are also useful for cytoprotection in neurodegenerative disorders, such as in the treatment of ischaemia (stroke).

Such compounds are useful in connection with transplant surgery and in treating conditions such as 35 rheumatoid arthritis, lupus, and other autoimmune diseases or diseases characterized by immune hyperfunction.

For use as discussed above, the compounds of formula I or the pharmaceutically acceptable salts thereof may be administered to a subject in need of treatment by a variety of conventional routes of administration, including oral, by injection, topical, and in an aerosol carrier composition for administration by breathing.

40 In general, the compounds of the formula I and the pharmaceutically acceptable salts thereof are most desirably administered in doses ranging from 0.1 mg. up to 100 mg. per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of pharmaceutical administration chosen. However, a dosage level that is in the range of from 0.3 mg to 10 mg per kg of body weight per day is most desirably employed. Nevertheless, variations may still 45 occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases, still larger doses may be employed without causing harmful side effects provided that such higher dose levels are first divided into several small doses for 50 administration throughout the day.

Although the compounds of formula I can be administered alone, they will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, oral administration may be in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the 55 form of elixirs or suspensions containing flavoring or coloring agents. In the case of animals, they are advantageously contained in an animal feed or drinking water. For parenteral injection, they may be used in the form of a sterile aqueous solution which may contain other solutes, for example enough salt or glucose to make the solution isotonic with blood.

The antipsychotic, antiinflammatory and immunosuppressive activity of the compounds of the formula I and the pharmaceutically acceptable acid addition salts thereof is demonstrated by the following examples.

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Example 1

In Vitro Binding

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Affinity of disclosed compounds for sigma receptors in brain tissue was ascertained by the degree of inhibition of binding of the sigma site radioligand, (+)-[<sup>3</sup>H]3-(3-hydroxyphenyl)-N-(1-propyl)piperidine ((+)-Largent et al., Proc. Natl. Acad. Sci. USA, 81:4983-87 (1984). Brains were removed from Sprague-Dawley CD male rats (Charles River Breeding Laboratories, Inc., Wilmington, MA; 200-300 g) following decapitation. Whole brain was homogenized in 25 volumes (v/w) of ice-cold 50 mM Tris (tris(hydroxymethyl)amino methane) hydrochloride pH 7.7 buffer using a Polytron PT-10 homogenizer. The pellet resulting from centrifugation of the homogenate at 45,000 x g for 10 minutes at 0-5° was washed twice by resuspension in the same volume of fresh buffer and recentrifugation. The final pellet was dispersed in 50 mM Tris hydrochloride pH 8.0 buffer (50 ml/g of original weight; "tissue preparation"). The incubation mixture in triplicate was comprised of 0.05 ml blank (10 M pentazocine for nonspecific binding), test compound or hydrochloride pH 8.0 buffer; and 0.75 ml tissue preparation. The latter was added just prior to incubation of the mixture at 25°C for 90 minutes. Afterwards, the mixture was diluted with 2.5 ml 10 mM Tris hydrochloride pH 7.7 buffer and filtered under vacuum through a Whatman GF/B glass-fiber filter (pretreated with 1% polyethyleneimine) in a Brandell cell harvester to recover the membranes. The filter was washed twice with the diluent buffer and placed in 10 ml Aquasol-2 (NEN<sup>R</sup> Dupont Co.) for determination of bound radioactivity in a liquid scintillation counter. Percent inhibition of specific (+)-[<sup>3</sup>H]3-PPP binding was calculated and the concentration inhibiting binding by 50% (IC<sub>50</sub>) was determined.

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Example 2

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In Vivo Binding

The efficacy of disclosed compounds for binding to brain sigma receptors in vivo was determined by comparing the labeling of these receptors in intact control and drug-pretreated mice with intravenously administered (+)-[<sup>3</sup>H]3-PPP. These experiments were conducted by the method of Koe et al. Eur. J. Pharmacol. 1989, In press. Mice (male Swiss albino from Charles River Breeding Laboratories, Inc., Wilmington, MA; 23-28 g) in groups of 5 received vehicle (controls) and 3 log doses of test compound intraperitoneally 30 minutes before an intravenous injection of (+)-[<sup>3</sup>H]3-PPP (400 Ci/kg). Five minutes later mice were killed by cervical dislocation and whole brains were removed and immediately frozen. Frozen brains were individually homogenized in 18 ml of ice-cold 50 mM Tris hydrochloride pH 8.0 buffer with a Polytron PT-10 homogenizer. Triplicate 1.0 ml aliquots were filtered under vacuum through Whatman GF/B filters to collect the membranes which were then washed with two 5-ml aliquots of 10 mM Tris hydrochloride pH 7.7 buffer. Membrane-bound radioligand (M) was determined by placing the filters in 10 ml Aquasol-R2 and measuring radioactivity in a liquid scintillation counter. Separate aliquots of the homogenates before filtration were assayed for total radioactivity (H) and protein content. The dose causing 50% inhibition of (+)-[<sup>3</sup>H]3-PPP binding in vivo (ID<sub>50</sub>) was estimated from semi-log plots of fraction bound (M/H), calculated as % control, versus dose.

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TABLE 1  
Inhibition of (+)-[<sup>3</sup>H]3-PPP Binding

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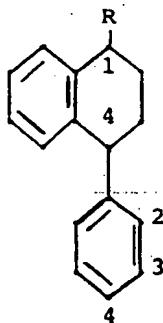
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Racemate	Substituents on Pendant Phenyl ring	R	IC <sub>50</sub> nM
(±)-trans	4-F	NHCH <sub>3</sub>	66
(±)-cis	4-Cl	NHCH <sub>3</sub>	33
(±)-trans	4-Cl	NHCH <sub>3</sub>	75
(±)-cis	3,4-diCl	NHCH <sub>3</sub>	19
(±)-trans	3,4-diCl	NHCH <sub>3</sub>	23
(±)-cis	3,4-diCl	N(CH <sub>3</sub> ) <sub>2</sub>	44
(±)-trans	3,4-diCl	N(CH <sub>3</sub> ) <sub>2</sub>	30
(±)-cis	2,4-diCl	NHCH <sub>3</sub>	29
(±)-cis	4-Br	NHCH <sub>3</sub>	13
(±)-trans	4-Br	NHCH <sub>3</sub>	85
(±)-trans	3-CF <sub>3</sub>	NHCH <sub>3</sub>	16
(±)-cis	4-CF <sub>3</sub>	NHCH <sub>3</sub>	5.9
(±)-trans	4-CF <sub>3</sub>	NHCH <sub>3</sub>	39
(±)-cis	3-CF <sub>3</sub> , 4-Cl	NHCH <sub>3</sub>	11
(±)-trans	3-CF <sub>3</sub> , 4-Cl	NHCH <sub>3</sub>	31

3 nM (+)-[<sup>3</sup>H]-3-PPP

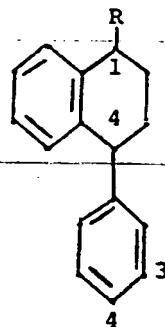
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TABLE 2  
Inhibition of (+)-[<sup>3</sup>H]3-PPP Binding



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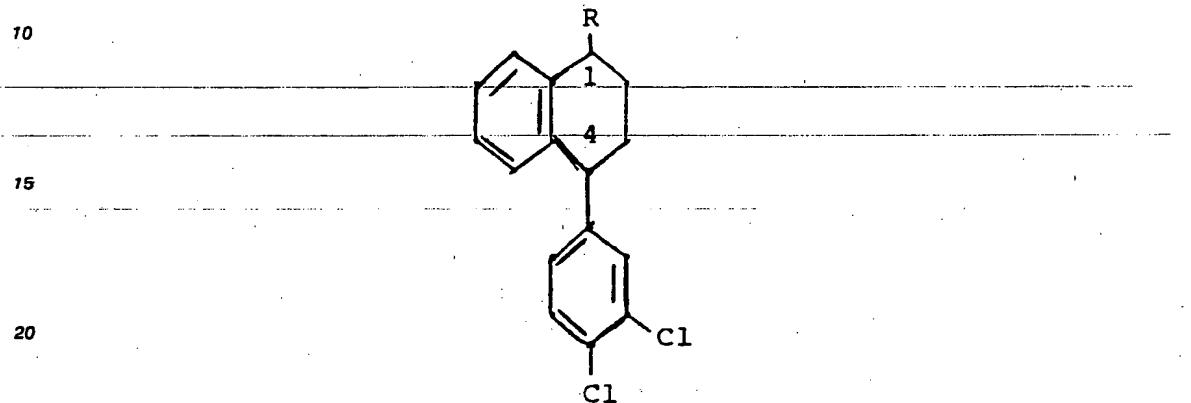
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Conformation	Substituents on Pendant Phenyl ring	R	IC <sub>50</sub> nM
(+)-1S, 4S	4-Cl	NHCH <sub>3</sub>	8.7
(+)-1S, 4S	3, 4-diCl	NHCH <sub>3</sub>	6.8
(-)-1R, 4R	3, 4-diCl	NHCH <sub>3</sub>	220
(+)-1R, 4S	3, 4-diCl	NHCH <sub>3</sub>	51
(-)-1S, 4R	3, 4-diCl	NHCH <sub>3</sub>	6.6
(+)-1S, 4S	3, 4-diCl	N(CH <sub>3</sub> ) <sub>2</sub>	28
(+)-1S, 4S	3, 4-diCl	NH <sub>2</sub>	58
(+)-1S, 4S	3-CF <sub>3</sub> , 4-Cl	NHCH <sub>3</sub>	17

3 nM (+)-[<sup>3</sup>H]3-PPP

5 TABLE 3  
 Inhibition of (+)-[<sup>3</sup>H]3-PPP Binding to Mouse Brain  
 In Vivo



25	Conformation	R	ID <sub>50</sub> mol/kg i.p.
30	(+)-1S,4S	NHCH <sub>3</sub>	0.72
	(-)-1R,4R	NHCH <sub>3</sub>	17
	(+)-1R,4S	NHCH <sub>3</sub>	3.6
35	(-)-1S,4R	NHCH <sub>3</sub>	0.43
	(+)-1S,4S	NH <sub>2</sub>	3.0

400 Ci/kg (+)-[<sup>3</sup>H]3-PPP i.v.

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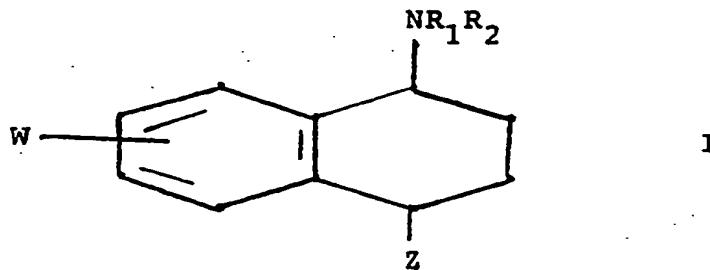
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Claims

55 1. The use of a compound of the formula

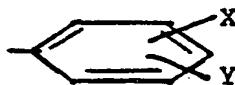
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or of a pharmaceutically acceptable acid addition salt thereof, wherein  
 R<sub>1</sub> and R<sub>2</sub> are each independently selected from hydrogen and C<sub>1</sub>-C<sub>3</sub> alkyl;  
 Z is

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20 wherein X and Y are each independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl, alkoxy of from 1 to 3 carbon atoms and cyano, with at least one of X and Y other than hydrogen; and  
 W is selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl and alkoxy of from 1 to 3 carbon atoms, for the manufacture of a medicament for the treatment of psychosis.

25 2. The use of a compound of the formula (I), or of a pharmaceutically acceptable acid addition salt thereof, as defined in claim 1, for the manufacture of a medicament for the treatment of inflammation and stroke and for use as an immunosuppressant.

30 3. Use as claimed in claim 1 for the treatment of schizophrenia, delusional disorder, brief-reactive psychosis, schizo-effective disorder, atypical psychosis, mania and in emotion discontrol in dementia.

4. Use according to any preceding claim wherein said compound is the cis or the trans isomer.

5. Use according to claim 4 wherein said compound is Cis(1S) (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

6. Use according to claim 4 wherein said compound is Cis(1S) (4S)-N-methyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

35 7. Use according to claim 4 wherein said compound is Cis(1S) (4S)-N-methyl-4-(3-trifluoromethyl-4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

8. Use according to claim 4 wherein said compound is Trans(1S) (4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

9. Use according to claim 4 wherein said compound is Trans(IR) (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

40 10. Use according to claim 4 wherein said compound is Cis(1R) (4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

11. Use according to claim 4 wherein said compound is Cis(1S) (4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

45 12. Use according to claim 4 wherein said compound is Cis(1S) (4S)-N,N-dimethyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

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⑯ Date of deferred publication of the search report:  
29.04.92 Bulletin 92/18

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⑯ Use of 4-phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives in the treatment of psychosis, inflammation, stroke and as immunosuppressants.

⑯ 4-Phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives have been found useful for the treatment of psychosis, inflammation, stroke and as immunosuppressants.

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EUROPEAN SEARCH REPORT

Application Number

EP 90 30 2365

DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)						
P, X	EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 165, nos. 2-3, 1989, pages 335-336, Elsevier Science Publishers B.V.(Biomedical Division): A. SCHMIDT et al.: "Sertraline potently displaces (+)-(3H)3-PPP binding to Sigma sites in rat brain" * The whole article *	1,3-5	A 61 K 31/135						
A	THE AMERICAN JOURNAL OF PSYCHIATRY, vol. 144, no. 11, November 1987, pages 1513-1514: M. LAPORTA et al.: "Hypomania induced by sertraline, a new serotonin reuptake inhibitor" * The whole article *	1-12							
A	THE JOURNAL OF CLINICAL PSYCHIATRY, vol. 49, supplement, August 1988, 'Serotonin in Behavioral Disorders', Proceedings of a Symposium, 21st November 1987, Zurich, pages 40-45; J. HEYM et al.: "Pharmacology of sertraline: A review" * Discussion *	1-12							
A	CLINICAL NEUROPHARMACOLOGY, vol. 11, no. 2, 1988, pages 105-119, Raven Press, Ltd., New York, US; S. I. DEUTSCH et al.: "The Sigma receptor: A novel site implicated in psychosis and antipsychotic drug efficacy" * Discussion *	1-12	A 61 K						
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>17-02-1992</td> <td>KLAVER T.</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	17-02-1992	KLAVER T.
Place of search	Date of completion of the search	Examiner							
THE HAGUE	17-02-1992	KLAVER T.							
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>							
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>									



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**CLAIMS INCURRING FEES**

The present European patent application comprised at the time of filing more than ten claims.

- All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims:
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

**LACK OF UNITY OF INVENTION**

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

See sheet -B-

- All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:



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EP 90 30 2365 -B-

**LACK OF UNITY OF INVENTION**

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1,3,4-12(partially) : Use of a compound of formula I for the treatment of psychotic disorders.
2. Claims 2,4-12(partially) : Use of a compound of formula I as antiinflammatory, immunosuppressant and against stroke.